~~12.~~ (Amended) ~~A nucleoside comprising a ribose~~ comprising a covalently attached electron transfer moiety (ETM) at the 2' position wherein said ETM is attached via a linker.

~~24.~~ (Amended) A nucleotide comprising a ribose comprising a covalently attached electron transfer moiety (ETM) at the 2' position wherein said ETM is attached via a linker.

REMARKS

Claims 12-25 are pending and under consideration in this case. Claim 23 has been canceled. Claims 12 and 24 have been amended to recite a limitation from canceled claim 23 wherein the ETM is attached to the 2' position using a linker. An Appendix of Pending Claims is attached for the Examiner's convenience.

As a preliminary matter, the Applicants thank Examiner Gary Jones for taking the time to interview this case on October 17, 2002.

Rejection Under 35 U.S.C. § 101: Lack of Asserted utility

Claims 12-25 are rejected under 35 U.S.C. § 101 for lack of specific asserted or a well established utility. The Examiner reiterates her rejection that the specification fails to teach the claimed "nucleoside comprising a covalently attached electron transfer moiety", and thus fails to disclose an asserted specific and substantial utility for the nucleoside. Specifically, the Examiner's position appears to be that Applicants invention is not useful because "one of skill in the art would not have expected that a nucleoside with attached electron transfer moiety which comprises a transition metal as known in the art and taught in the specification would be readily incorporated during either an enzymatic or chemical synthesis due to the bulky structure of such electron transfer groups which would interfere with the necessary contact between the reactants". Applicants respectfully disagree.

The Examiner's basic point does not appear to be that the nucleosides are not useful per se, but that since the Examiner questions whether they can be incorporated into nucleic acids, they cannot be useful unless this property has been shown.

General principles governing utility rejections are set forth in M.P.E.P. § 2107. According to the guidelines, an invention has a well established utility if (i) a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention (e.g., properties or applications of a product or process) and (ii) the utility is specific, substantial, and credible. If an applicant has asserted that the claimed invention is useful for a particular practical purpose and the assertion would be considered credible by a person of ordinary skill in the art, a rejection based on lack of utility should not be imposed.

As outlined below, Applicants respectfully submit that a person of ordinary skill in the art would immediately appreciate why the invention is useful and that they have provided a credible assertion of specific and substantial utility.

The Applicants submit that a person of ordinary skill in the would find their assertion of specific and substantial utility creditable. Credibility is assessed from the perspective of one of ordinary skill in the art in view of the disclosure and any other evidence of record (e.g., test data, affidavits or declarations from experts in the art, patents, or printed publications) that is probative of the Applicant's assertions. An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement.

Applicants assert that a person of ordinary skill in the art would know that modified nucleosides with "bulky groups" such as transition metals and other labels such as "bulky" fluorescent molecules attached to the base could be incorporated during enzymatic or chemical synthesis of nucleic acids. Applicants present several articles in support of their

position that nucleosides with "bulky" substitutents attached at the base would be known to a person of ordinary skill in the art to be incorporated into nucleic acids. The applicants are not using subsequent work to supplement the disclosure of the application; rather, the subsequent work is presented to show that the utility asserted and shown in the application is supported by further research, and that the specification fully enables the synthesis of metal containing nucleosides. See In re Wilson, 135 USPQ 442, 444 (CCPA 1962); Ex parte Obukowicz, 27 USPQ 2d 1063 (BPAI 1993); Gould v. Quigg, 3 USPQ 2d 1302,1305 (Fed. Cir. 1987):

> "it is true that a later dated publication cannot supplement an insufficient disclosure in a prior dated application to render it enabling. In this case the later dated publication was not offered as evidence for this purpose. Rather, it was offered . . . as evidence that the disclosed device would have been operative"printed publications.

A chapter published in a commercially available Handbook by Molecular Probes, namely: "Chemically modified nucleotides, oligonucleotides and nucleic acids": Chapter 8-Section 8.2 in the 'Handbook of Fluorescent probes and Research chemicals' by Richard P. Haugland, 6th edition (attached hereto as Exhibit A) describes fluorophore labeled (bulky adducts; see Fig. 8.4 and Table 8.2) nucleosides and oligonucleotides, that is, chromatide nucleotides, for enzymatic incorporation into nucleic acids (see page 157, column 1, line 18-21).

Articles by Meade and Kayyem (1995) Angew. Chem. Int. Ed. Engl. 34: 352-353 (attached as Exhibit B), Yu et al. (2001) J. Org. Chem., 66:2937-2942 (attached as Exhibit C); Krider, et al (2001) Inorg. Chem., 40: 4002-4009 (attached as Exhibit D); Hwang and Greenberg, (1999) Organic Letters, 1: 2021-2024 (attached as Exhibit E); Hwang and Greenberg, (2001) J. Org. Chem., 66: 363-369 (attached as Exhibit F) Tsuneo, et al., (2000) Tetrahedron Letters, 41: 2605-2608 (attached as Exhibit G) describe modified nucleosides labeled with bulky substitutents, such as fluorophores, transition metal complexes, etc., at the 2' position of ribose for incorporation into nucleic acids both enzymatically and chemically.

Modified nuclosides labeled at the 5' position with bulky substitutents are also known. See for example, CA registry number 255852-09-6; 454464-20-1282543-35-5; 182005-99-8; 126139-47-7; and, 161016-72-4 (attached as Exhibit H).

Taken together, these Exhibits show that "bulky" substitutents were known to be incorporated into nucleic acids, both enzymatically and chemically, both prior to and after the invention.

In further support of this position, , Applicants submit the declaration by Dr. Thomas J. Meade. As set forth in paragraph 1, Dr. Meade is a Professor Of Chemistry; Biochemistry and Molecular and Cell Biology; and, Neurobiology and Physiology at Northwestern University. As can be seen from Dr. Meade's curriculum vitae (attached as Declaration Exhibit A), Dr. Meade has extensive experience in designing and synthesizing modified nucleosides.

As set forth in paragraph 7, Dr. Meade states that it is his belief that a person of skill in the art would understand that the present invention has a specific use, i.e., the provision of modified nucleosides for use as gene probes in the electrochemical detection systems outlined in the specification. As set forth in paragraphs 9-10, Dr. Meade states that it is his belief that nucleosides with bulky substituents at a variety of positions are known to be incorporated into nucleic acids.

As can be seen from the above discussion, a person of ordinary skill in the art would immediately appreciate that these claimed compounds can be made and used as gene probes. Accordingly, Applicants submit that there is a specific asserted utility for the present invention and respectfully request withdrawal of the rejection of Claims 12-22 and 24-25 under 35 U.S.C. § 101.

Rejection Under 35 U.S.C. § 112, first paragraph: Lack of Enablement

Claims 12-25 are rejected under 35 U.S.C. § 112, first paragraph for a lack of enablement based on the finding that the claims are not supported by a specific asserted utility or a well-established utility. In view of the discussion above, Applicants have enabled their invention with adequate support in the specification and with exhibits attached hereto. Thus, one skilled in the art is fully enabled to make and use this invention.

Accordingly, Applicants respectfully request withdrawal of the rejections to Claims 12-25 under 35 U.S.C. 112, first paragraph for lack of enablement.

Rejection Under 35 U.S.C. § 112, first paragraph: Lack of Written Description

Claims 12-25 are rejected under 35 U.S.C. 112, first paragraph for lack of written description of subject matter to reasonably convey to persons skilled in the art that applicant had possession of the claimed invention at the time of filing of the application. Specifically, the Examiner contends that the specification fails to describe "nucleoside (or nucleotide) comprising a covalently attached transfer moiety". Basically, the Examiner's position appears to be that while these compounds are specifically disclosed, pointing to Figures 4A and 4B, these "bulky" adducts are not enabled and thus the Applicants did not have possession of the invention. Applicants respectfully traverse.

The essential purpose of the written description requirement is to show the possession of the invention as of the filing data as a *prima facie* date of invention. *In re Smith*, 481 F.2d 910, 178 U.S.P.Q. 620, 623 (CCPA 1973). Accordingly, the specification is required to contain a statement that adequately describes the invention as claimed. However, the invention need not be described in *ipsis verbis* in order to satisfy the description requirement. See *In re Luckach, Olson, and Spurlin*, 169 U.S.P.Q. 795, 796 (CCPA 1971). It is sufficient to satisfy the written description requirement if the

> specification contains a statement of appellant's invention which is as broad as appellant's broadest claims . . . .

In re Robins, 420,F.2d 452, 166 U.S.P.Q. 552,555 (CCPA 1970).

> It is only required, for example, that the specification describe the invention sufficiently for those of ordinary skill in the art to recognize that the applicant invented the subject matter he now claims.

In re Voss, 557 F.2d 812, 194 U.S.P.Q. 267,271 (CCPA 1977).

In view of the evidentiary function of the written description requirement and the relative ease with which it is met, it is not surprising that description requirement must be found, specifically or inherently, within the specification and original claims.

Applicants submit that the specification as filed provides a legally sufficient written description for both nucleosides modified at the 2' position and their site-specific addition of these modified nucleosides into a growing oligonucleotide. Basically the method comprises the following steps for attachment of an electron transfer moiety to a ribose: 1) preparation of a modified nucleoside (see page 20, lines 6-9, and 13-16); 2) addition of an ETM (see page 20, lines 10-13); and 3) incorporation of the of the modified nucleoside into a growing oligonucleotides by standard synthetic techniques (e.g. phosphoramidite chemistry; see page 20, lines 25-27).

Applicants point to Figures 4A and 4B to show that applicant contemplated a nucleoside comprising a covalently attached electron transfer moiety at the time the invention was filed. Additional support that the addition of metals, additional ligands and ETMs to a nucleoside prior to incorporation into a growing nucleic acid chain was contemplated is found in the specification at page 23, lines 23-31:

> As described above, the electron transfer moiety, preferably a transition metal complex, may be attached to any of the five bases (adenine, thymine, uracil, cytosine, guanine and other non-naturally occurring bases such as inosine, xanthine, and hypoxanthine, among others). This is done using well known techniques; see Telser et al., J. Am. Chem. Soc. 111:7226-7232

(1989); Telser et al., J. Am. Chem. Soc. 111:7221-7226 (1989). As outlined herein, these terminally modified nucleosides may be attached to the nucleic acid enzymatically as is known in the art, using DNA polymerases; alternatively, the modified nucleosides may be incorporated into a growing oligonucleotide chain using traditional phosphoramidite chemistry during oligonucleotide synthesis as is outlined herein.

Applicants enclose a number of publications to show that methods were developed that allowed chemical modification of oligonucleotides at the terminal phosphates, and at both internal and terminal bases with "bulky groups" such as transition metals and other labels such as "bulky" fluorescent molecules.

One such example, is the incorporation of a ruthenium compound to an internal base in a DNA octomer (*See* Telser, et al., *J. Am. Chem. Soc.*, 111:7221-7226 (1989) attached hereto as Exhibit I). Other examples include the construction of a 5'-dye-labeled nucleoside phosphoramitide reagent for use as primers in a modified Sanger protocol (U.S. Patent No. 4,415,732, attached hereto as Exhibit J). Sinha and Striepke describe methods of synthesizing oligonucleotides with reporter groups, such as fluorophores, chromophores, biotin, etc., using solid-phase phosphoramidite chemistry (Sinha and Striepeke (1991) "Oligonucleotides with reporter groups attached to the 5'-terminus", In Oligonucleotides and Analogues, ed. F. Exkstein, Oxford University Press, Oxford, pp 185-210; attached hereto as Exhibit K). Conway, et al., describe the sequence-specific attachment of reporter molecules to the backbone of DNA using internal phosphodiesters (Conway, et al. (1991) "Site-specific attachment of labels to the DNA backbone", In Oligonucleotides and Analogues, ed. F. Exkstein, Oxford University Press, Oxford, pp 211-239; attached hereto as Exhibit L).

In addition, Applicants submit the declaration of Dr. Meade. In paragraph 12, Dr. Meade states that it is his belief that the specification supports and contemplates the addition of metals, additional ligands and ETMs to a nucleoside prior to incorporation into a growing nucleic acid chain as well as after the modified nucleoside is so incorporated.

Dr. Meade basis his opinion on (1) the description of modified nucleosides as disclosed in Figures 4A and 4B; (2) the disclosure in the specification found at page 23, lines 23-31; and (3) his knowledge of the existing art.

Since the current specification must be read in view of the existing art, the Examiner's presumption that "incorporation of nucleosides comprising bulky adducts like ETMs into nucleic acids using enzymatic synthesis would not be expected by one of skill in the art" is incorrect. According, Applicants request withdrawal of the rejection.

Attached hereto is a marked up version of the changes made to the claims and specification by the current amendment. The attached page is captioned "**Version with Markings to Show Changes Made.**"

The Examiner is invited to contact the undersigned at (415) 781-1989 if any issues may be resolved in that manner.

Respectfully submitted,

DORSEY & WHITNEY LLP

Dated: 10/29/02

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

12. (Amended) A nucleoside comprising a ribose comprising a covalently attached electron transfer moiety (ETM) at the 2' position wherein said ETM is attached via a linker.

24. (Amended) A nucleotide comprising a ribose comprising a covalently attached electron transfer moiety (ETM)at the 2' position wherein said ETM is attached via a linker.

Appendix of Pending Claims

12. A nucleoside comprising a ribose comprising a covalently attached electron transfer moiety (ETM) at the 2' position wherein said ETM is attached via a linker.

13. A nucleoside according to claim 12 wherein said electron transfer moiety is an organic electron transfer moiety.

14. A nucleoside according to claim 12 wherein said electron transfer moiety is a transition metal complex.

15. A nucleoside according to claim 12 wherein said transition metal complex comprises ruthenium.

16. A nucleoside according to claim 12 wherein said transition metal complex comprises iron.

17. A nucleoside according to claim 12 wherein said transition metal complex comprises osmium.

18. A nucleoside according to claim 12 wherein said transition metal complex comprises rhenium.

19. A nucleoside according to claim 12 wherein said transition metal complex comprises cobalt.

20. A nucleoside according to claim 12 wherein said transition metal complex comprises palladium.

21. A nucleoside according to claim 12 wherein said transition metal complex comprises platinum.

22. A nucleoside according to claim 12 wherein said electron transfer moiety is attached via an amine group at said 2' position.

24. A nucleotide comprising a ribose comprising a covalently attached electron transfer moiety (ETM)at the 2' position wherein said ETM is attached via a linker.

25. A nucleic acid comprising a nucleoside comprising a ribose comprising a covalently attached electron transfer moiety at the 2' position.

B